REMARKS/ARGUMENTS

Allowed Claims

Applicants with to thank the Examiner for indicating that claims 1, 2, 4, 8, and 12-14 are deemed allowable.

35 U.S.C. § 112

It is believed that the crux of the rejection of claim 9 is set forth on page two of the January 15, 2004 office action. Specifically, the Examiner is referred to the passage:

> ...the specification only appears to provide examples of treating pain as opposed to preventing pain and it *does not appear from the prior art of record that prevention of pain is highly predictable.* As such, it appears that one of ordinary skill in the art would be required to do undue experimentation in order to show that the claimed compounds prevent pain (emphasis added).

Applicants respectfully disagree and request that the Examiner consider the following:

The assays described in Example 22 and Example 23 of the application establish an unmistakable link between the claimed compounds and mGluR5 receptor antagonism. The Example 24 animal study establishes that these same compounds reduce pain. Considered together, Examples 22, 23 and 24 demonstrate that mGluR5 receptor antagonism reduces or lessens the current perception of pain.

The claimed compounds antagonize the mGluR5 receptor independent of whether pain is perceived at a particular moment. A patient whose mGluR5 receptors are actively being antagonized by a claimed compound will be *prevented* from feeling pain, or prevented from feeling as much pain, when (otherwise) painful stimuli or conditions do occur. This *preventative* effect will last as long as there is a sufficient degree of mGluR5 antagonism occurring. Put more simply, as long as enough mGluR5 receptors are being antagonized, perception of pain will be prevented.

Applicants take issue with the Examiner's conclusion that "it does not appear from the prior art of record that prevention of pain is highly predictable". The Examiner has cited absolutely no

teachings in the prior art to support this conclusion. To the contrary, numerous commercial pain remedies are routinely prescribed and effectively used for the *prevention* of the *anticipated* onset of pain. Examples of such remedies include anesthetics for the prevention of pain from surgery, dentistry and childbirth; β-blockers and anti-depressants for the prevention of migraine or cluster headache pain; prophylactic pain medication for reducing the need for post-operative narcotics in children; NSAIDs taken prior to vigorous exercise such as long-distance running or triathlons; and numerous treatments for premenstrual/menstrual pain. A medical doctor or other health care professional seeking to prevent the onset of pain symptoms in a patient, or the patient him/herself, is in a position to know when these and other pain symptoms are likely to occur and then act to prevent this pain.

Further, we reiterate that "prevention" is not understood in the art to mean "that the subject will *never again* suffer pain or that the drug prevents pain *no matter what* the cause". Rather, one skilled in the art would understand (1) that "prevention" relates to those pain conditions wherein the mGluR5 receptor plays a role, and (2) that the duration of the preventative effect would not be unlimited but would be limited by the pharmacological properties of the compound.

In this regard, the undersigned wishes to point out to the Examiner that the *Examiner himself* has in the past, and recently, allowed claims directed to prevention. Specifically, the Examiner allowed claims 37 and 40 of U.S. Patent No. 6,274,570 B1, directed to a "method of preventing infestation" with a particular composition, yet there are no examples in this patent showing prevention. More recently, there is U.S. Patent No. 6,503,944 B1 wherein the Examiner allowed claim 11 directed to "... a method of preventing water loss from the skin". Here again there are no data or examples establishing the prevention of water loss, yet the claims were allowed. Similarly, the Examiner's supervisor, as recently as *last month*, allowed "prevention" claims in U.S. Patent No. 6,699,492 B2, claim 33. This patent contains no data or examples even relating to prevention.

Not only are "prevention" claims allowed in the '570, '944 and '492 patents, but there is also no limiting language as to the duration of the prevention or the cause of the condition being prevented. Applying the Examiner's instant position to the '944 patent, one would suppose that the user of the claimed skin care composition will never again suffer water loss no matter what the cause. This, of course, does not make sense. It is requested that the Examiner read the claims in this application with the same common sense understanding of the term "prevention" as he did in the above-cited patents. Copies of the '570, '944 and '492 patents are enclosed.

Regarding the rejections of claims 15 and 16 for alleged lack of enablement, the Examiner is asked to consider that mGluR5 has been linked to the treatment of these disease conditions in the scientific literature including anxiety and depression,[1-6] Parkinson's disease,[7-9] drug dependence,[10] stroke/brain trauma[11,12] and mental retardation.[13]. Thus, it is submitted that treatment of the claim 15 and 16 conditions is in fact enabled. Copies of all of these references are enclosed. For the Examiner's convenience, a listing of the same references follows these remarks.

Conclusion

In view of the above remarks, Applicants respectfully submit that the application is in condition for allowance and request a Notice to that effect. Attorney for Applicants can be reached at the telephone number and address below. Correspondence should be sent to the address below.

Please deduct the appropriate fees or deficiency in fees required from Merck Deposit Account No. **13-2755**.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date appearing below.

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By Kathy Reynolds Date 4.15.04

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References

(1) Cosford, N. D. P.; Tehrani, L.; Roppe, J.; Schweiger, E. J.; Smith, N. D. et al. 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine: A Potent and Highly Selective Metabotropic Glutamate Subtype 5 Receptor Antagonist with Anxiolytic Activity. *J. Med. Chem.* **2003**, *46*, 204-206.

(2) Brodkin, J.; Busse, C.; Sukoff, S. J.; Varney, M. A. Anxiolytic-like activity of the mGluR5 antagonist MPEP. A comparison with diazepam and buspirone. *Pharmacology, Biochemistry and Behavior* **2002**, *73*, 359-366.

(3) Spooren, W. P. J. M.; Vassout, A.; Neijt, H. C.; Kuhn, R.; Gasparini, F. et al. Anxiolytic-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)pyridine in rodents. *Journal of Pharmacology and Experimental Therapeutics* **2000**, *295*, 1267-1275.

(4) Pilc, A.; Klodzinska, A.; Branski, P.; Nowak, G.; Palucha, A. et al. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. *Neuropharmacology* **2002**, *43*, 181-187.

(5) Tatarczynska, E.; Klodzinska, A.; Chojnacka-Wojcik, E.; Palucha, A.; Gasparini, F. et al. Potential anxiolytic- and antidepressant-like effects of MPEP, a potent, selective and systemically active mGlu5 receptor antagonist. *British Journal of Pharmacology* **2001**, *132*, 1423-1430.

(6) Schulz, B.; Fendt, M.; Gasparini, F.; Lingenhohl, K.; Kuhn, R. et al. The metabotropic glutamate receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) blocks fear conditioning in rats. *Neuropharmacology* **2001**, *41*, 1-7.

(7) Ossowska, K.; Konieczny, J.; Wolfarth, S.; Wieronska, J.; Pilc, A. Blockade of the metabotropic glutamate receptor subtype 5 (mGluR5) produces antiparkinsonian-like effects in rats. *Neuropharmacology* **2001**, *41*, 413-420.

(8) Spooren, W. P. J. M.; Gasparini, F.; Bergmann, R.; Kuhn, R. Effects of the prototypical mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine on rotarod, locomotor activity and rotational responses in unilateral 6-OHDA-lesioned rats. *European Journal of Pharmacology* **2000**, *406*, 403-410.

(9) Breysse, N.; Baunez, C.; Spooren, W.; Gasparini, F.; Amalric, M. Chronic But Not Acute Treatment with a Metabotropic Glutamate 5 Receptor Antagonist Reverses the Akinetic Deficits in a Rat Model of Parkinsonism. *J. Neurosci.* **2002**, *22*, 5669-5678.

(10) Chiamulera, C.; Epping-Jordan, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C. et al. Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nature Neuroscience* **2001**, *4*, 873-874.

(11) Allen, J. W.; Vicini, S.; Faden, A. I. Exacerbation of Neuronal Cell Death by Activation of Group I Metabotropic Glutamate Receptors: Role of NMDA Receptors and Arachidonic Acid Release. *Experimental Neurology* **2001**, *169*, 449-460.

(12) Bao, W. L.; Williams, A. J.; Faden, A. I.; Tortella, F. C. Selective mGluR5 receptor antagonist or agonist provides neuroprotection in a rat model of focal cerebral ischemia. *Brain Research* **2001**, *922*, 173-179.

(13) Huber, K. M.; Gallagher, S. M.; Warren, S. T.; Bear, M. F. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 7746-7750.